

**35 USC § 112, First Paragraph Rejection**

Claims 1-14 stand rejected under 35 USC § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection. However, given that the Examiner's arguments are directed to an alleged need for undue experimentation, this rejection will be addressed as an enablement rejection.

The Examiner contends that the specification fails to provide the guidance that one of skill in the art would need in order to practice the claimed invention. Applicants respectfully disagree. The Examiner is incorrect in assuming that the Examples are prophetic. The Examples were performed prior to filing. This is clear upon reading pages 14-21 of the specification. Further, the specification discloses all of the information that one of ordinary skill in the art would need in order to practice the claimed invention, thus Examples are not necessary. Notwithstanding, the Examples been provided by the Applicants and are not prophetic. Given these Examples and the general teaching of the specification, one of ordinary skill in the art would be able to practice the claimed invention. As such, Applicants respectfully request that the current rejection under 35 U.S.C. 112, first paragraph be withdrawn.

**35 USC § 112, Second Paragraph Rejection**

Claim 1-14 stands rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claim 1 was said to be indefinite in its recitation of the phrase "optionally mixing said first granulate with one or more further components". Applicants respectfully disagree. This phrase is clear and understandable to one skilled in the art as the identity of potential further components is disclosed throughout the specification of the instant application. See, for example, page 9, lines 8-15 of the specification, Example 2 on page 15 of the specification and, claim 13 as originally filed. Given this disclosure and the level of skill in the art at the time the application was filed, one of ordinary skill in the art would clearly understand the metes and bounds of the claims of the instant application. Accordingly, the rejection of claim 1 under 35 U.S.C. § 112, second paragraph, is respectfully requested to be withdrawn in view of the foregoing discussion.

The Examiner states that claim 6 lacks antecedent basis for the phrase "in step (i) the same material is used as said diluent and as said binder". Claim 6 has been amended in order to provide a nexus between this phrase and claim 3. Accordingly, the rejection of claim 6 under 35 U.S.C. § 112, second paragraph, is respectfully requested to be withdrawn.

The Examiner states that in claims 4 and 5 the terms "68 to 80% wt" and "60 to 95% wt." are unclear. Applicants respectfully disagree. The terms "68 to 80 %wt and "60 to 95% wt" are clear and signify a percentage of the total weight ratio. Given the teachings of the specification, one of ordinary skill in the art would clearly understand these terms and as such would understand the metes and bounds of the claimed invention. Accordingly, the rejection of claims 4 and 5 under 35 U.S.C. § 112, second paragraph, is respectfully requested to be withdrawn.

The Examiner states that claim 12 lacks antecedent basis for the phrase "first granulate has a particle size distribution of". Claim 12 has been amended in order to provide a nexus between this phrase and claim 3. Accordingly, the rejection of claim 12 under 35 U.S.C. § 112, second paragraph, is respectfully requested to be withdrawn. The Examiner contends that claims 8 and 13 set forth improper Markush terminology. These claims have been amended in accordance with the suggestions of the Examiner. Accordingly, the rejection of claims 8 and 13 under 35 U.S.C. § 112, second paragraph, is respectfully requested to be withdrawn.

### **35 U.S.C. § 103(a) Rejection**

Claims 1-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Valentine (EP 0192460) in view of Walsdorf et al. (U.S. Patent 4,814,177). This rejection is respectfully traversed. Applicants respectfully contend that the combined teachings of Valentine and Walsdorf do not contain each and every element of the claimed invention. Further, these references do not provide the motivation that one of

ordinary skill in the art would need to combine them and in fact teach away from the claimed invention.

Valentine is silent on the nature of the calcium carbonate that is suitable to be used in the process of the invention. The sole requirement in Valentine for the process is that the particle size of the calcium carbonate is between 3 and 10 microns. In the Examples it is further specified that the calcium carbonate is food grade (Example XIX, page 33) or USP (Example XX, page 33). The citation gives no indication of the structure or crystallinity and surface area of the calcium carbonate used. In the process of the current application, the nature of the surface area crystallinity is exceptionally important, and is thus recited in claim 1. Further, the process disclosed in Valentine produces agglomerates which have a zeolite structure (a 3D honeycomb-like structure). However, the granulate produced by the process of the present invention does not have a zeolite structure.

On page 2, line 26 onwards of the specification as filed, it is recited that the physical characteristics of the calcium compound are important. On page 3, line 3, it states that the crystallinity and low surface area of the calcium compound are particularly important when it comes to processing as in claim 1. The surface area as specified in claim 1 of the current invention is 0.1 to 1.2 m<sup>2</sup>/g.

As shown in Figures 7 and 8 of the current application, in the granulates made according to the process with calcium compounds of the correct nature, the granulate is

formed with regular particles with a porous structure. Clearly, the structure is determined by the geometrically regular, e.g. cubic or pseudocubic crystal shapes. The individual crystals are glued together by binder to form granules.

In order to demonstrate the importance of the specific surface area of the calcium compound, as explained below the Applicant has carried out further investigations, particularly with reference to Example XIII of Valentine. It is also further explained below why agglomeration of calcium carbonate will not occur in Example XIII D of Valentine.

1. Example XIII D of Valentine - Composition and process

Applicants believe there may be a printing mistake with respect to the liquid binder flow rate and that this should be 300 ml/min instead of 30 ml/min. This is based on the fact that Example XIII is stated to have been processed as described in Example I where the liquid flow rate is 300 ml/min (page 24, line 12) having regard to page 19, line 11 where it is stated that the preferred flow rate is 300 ml/min. Moreover, the atomizing airflow rate is stated to be the same (170 m<sup>3</sup>/hr) for Examples I and XIII. On page 19 it is also stated that the liquid binder flow rate in general ranges from 60 ml/min to 1200 ml/min.

There is a 200-fold decrease in the batch size from Examples XIII A-C (60 kg) (which is comparable to that in Example I) to Examples XIII D-E (300g).

From general knowledge of fluid bed granulation theory and practice it is not possible to vary the batch size in this manner without modifying other process parameters and still be able to produce a successful and agglomerated product. This is due to the fact that there will not be sufficient particle material in the fluidized bed with a 300g batch and the spray from the spray nozzles will go directly on to the walls in the fluid bed container and be deposited there.

In Example XIII it is further specified that 10 liters of 10% w/w maltodextrin solution is used which is equivalent of 1000g of maltodextrin as dry matter. As the batch size is only 300g, this clearly indicates that Examples XIII D and E either were not actually carried out (i.e. were "prophetic" examples) or that they were carried out using different unspecified apparatus and processing conditions.

From the composition of Example XIII D it can be calculated that the actual amount of maltodextrin in the formula is 6.6 gram which constitutes 66 grams of granulation liquid. At a spray rate of 300 ml/min, 66 gram of granulation liquid will be sprayed out in a matter of 13 seconds. This again makes no sense, as a fluidized powder bed needs a prolonged spraying phase in order to build up the granules in the agglomerate.

One thus has to conclude that the information given in Example XIII and elsewhere in Valentine does not enable the skilled man to carry out Examples XIII D and E.

2. The importance of the specific surface area of calcium carbonate

The commercially available calcium carbonates used in the current invention have been selected on account of their low specific surface area (in the range of 0.1 to 1.2 m<sup>2</sup>/g - claim 1 (i)). In order to prove that it is indeed the physical nature of the calcium compound that is important in the process of the invention, the Applicant has performed a series of experiments, in order to show that calcium compounds with a mean particle size in the range described in citation, but with a higher surface area, would not be suitable for using in the process of the application.

The fluid bed batches had the following compositions:

Calcium carbonate:	74.2%
Sorbitol:	23.2%
PVP:	2.6%

The particle size and distribution was analyzed by Malvern Mastersizer 2000. The different types of calcium carbonate were analyzed as liquid suspensions, and the granulates as dry preparations in an air stream. The mean particle size was measured

using the equivalent volume diameter  $D[4,3]$  which is the arithmetic mean diameter and by the volumetric median  $d[0.5]$  where 50% of the particles are above and below the mean diameter. The specific surface area was measured by a Carlo Erba Sorptomatic 1900 and a Sartorius microbalance (Institute for Ind. Chemistry, Sintef, Trondheim). The bulk density measurements were performed according to Ph.Eur.

The following processing parameters were used for all the fluid bed trials:

Batch size: 3 kg  
 Granulation liquid: 28% PVP (K30)  
 Inlet air temp.: 45°C  
 Spray rate: 40 g/min  
 Total granulation liquid: 280 g  
 Product temperature: 23 - 26°C  
 Inlet air temp. drying: 70°C  
 End point product temp. 44°C

Five different qualities of calcium carbonate have been included in this evaluation and the results shown in Table 1 below.

Table 1: Calcium carbonate used in investigation

Quality	Bulk Density (g/ml)	Specific Surface Area (m <sup>2</sup> /g)	Mean Particle Size $d[0.5]$ (μm)
Pharmaceutical CaCO <sub>3</sub>	1.14	0.5	17.4
Scoralite 1A+B	1.03	0.3	17.0
Heavy PCC (Specialty Min.)	0.76	1.0	13.9
Sturcal L (Specialty Min.)	0.57	3.4	9.2
Sturcal H (Specialty Min.)	0.44	5.6	9.3



There are two distinct groups of types of raw calcium carbonate with respect to the specific surface area where the first three types of calcium carbonate have specific surface area values in the range of 0.3 to 1.0 m<sup>2</sup>/g and the last two types of calcium carbonate have specific surface area values in the range of 3.4 to 5.6 m<sup>2</sup>/g.

Only the first three types of calcium carbonate fulfill the requirements set out by claim 1 of the current application: they have a mean particle size in the range of 3 to 40 µm and have a surface area of 0.1 to 1.2 m<sup>2</sup>/g. The other types of calcium carbonate have the correct particle size but their specific surface area is too large to fall within the scope of claim 1.

The purpose of agglomeration of powder blends into granulates are many, but the main aims are to reduce the amount of dust, increase the ease of flow of the granulate in process machinery and to facilitate the tableting process. A satisfactory agglomeration is evident when the mean particle size is significantly increased and this is accompanied by a reduction of the bulk density. The reduction of the bulk density is due to the fact that the particles after agglomeration will be more loosely packed with less fine material to fill the voids in the granulate.

Five fluid bed batch experiments were carried out with various types of calcium carbonate which had different specific surface area and with a particle size in the range of 5 to 20 µm.

Table 2: Results of fluid bed experiments

## Particle Size Distributions

Batch No.	Calcium carbonate type	d[0.1]( $\mu\text{m}$ )	d[0.5]( $\mu\text{m}$ )	d[0.9]( $\mu\text{m}$ )	d[4.3]( $\mu\text{m}$ )
1 (granulate)	Scora 1A+B	13.0	83.1	243.2	108.0
1(Powder mixture prior to granulation)	Scora 1A+B	7.0	20.8	160.8	55.2
2 (granulate)	Pharm. $\text{CaCO}_3$	13.4	90.8	249.4	111.8
3 (granulate)	Heavy PCC	9.7	76.2	228.5	98.2
4 (granulate)	Sturcal L	5.1	16.9	190.9	65.2
4 (Powder mixture prior to granulation)	Sturcal powder mixture	2.1	12.4	161.7	50.7
5 (granulate)	Sturcal H	4.5	24.4	212.2	78.4

As can be seen from Table 2 the first three types of calcium carbonate (which have lower specific surface area values) have all achieved a satisfactory agglomeration.

The particle size and distribution was measured for the powder mixture of two of the batches (shown as d[0.1], d[0.5] and d[0.9]). The mean particle size for the powder mixtures prior to granulation has increased slightly from the values given on Table 1.

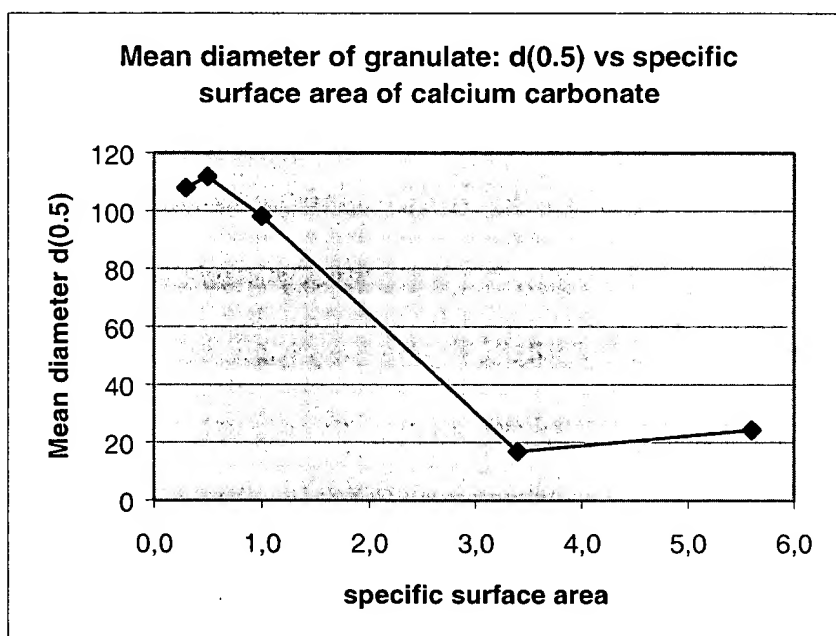
This is due to the addition of sorbitol to the mixture, which has a larger particle size.

Batch 1 prior to processing had a mean particle size of 20.8 $\mu\text{m}$ . After processing it can be seen that the particle size is 83.1  $\mu\text{m}$ ; for batch 4 processing only raised the mean

particle size from 12.4  $\mu\text{m}$  to 16.9 $\mu\text{m}$ , which is a much smaller increase in particle size.

Thus, batch 1 has achieved satisfactory agglomeration, whereas batch 4 has not.

Both the batches with higher specific surface areas (4 and 5) were difficult to process in the fluid bed due to uneven fluidization and adherence to the internal surfaces of the expansion chamber and product container. These results are further depicted in diagram 1.



Representative batches were further characterized by evaluating the change in the bulk densities between the powder blends and the agglomerated product.

Table 3: Change in bulk density

Type	Batch no.	Bulk Density of powder blend	Bulk Density of granulate

Scora 1A+B	1	0.96	0.60
Sturcal L	4	0.64	0.65

A significant reduction of the bulk density occurred for the batch containing a calcium carbonate source with a lower surface area as opposed to the batch containing a calcium source with a higher specific surface area where no change has occurred.

These results demonstrate that it is the combination of particle size and specific surface area which is crucial for a successful granulation outcome in a fluid bed. Only batches containing calcium compound with a specific surface are inside the range of 0.1 to 1.2 m<sup>2</sup> achieved a satisfactory agglomeration based on an increase of the mean particle size and a reduction of the bulk density. The specific surface area of the calcium compound is of vital importance for the quality of the granulate and in order to achieve a short process time. Calcium compounds with a high specific surface area require much more granulation liquid in order to be sufficiently wetted or to achieve enough liquid bridges and stable bonds between the particles.

The great majority of commercially available calcium carbonate compositions exhibit a specific surface area above 1.2 m<sup>2</sup>/g. It has been shown that with the fluid bed process in the claimed invention it is not possible to achieve a satisfactory agglomeration with calcium carbonate qualities exhibiting a high value for the specific surface area.

Thus, it is vital to understand that one cannot take any type of calcium carbonate and expect that one can achieve a satisfactory and efficient fluid bed agglomeration. The

quality of calcium carbonate has to be chosen based on both the particle size/distribution, crystal shape and the specific surface area. Not paying attention to the specific surface area and crystal shape of the calcium carbonate crystals will most probably result in unsatisfactory agglomeration where a large part of the agglomerate will contain fines and be sieved away. Thus, Example XIII of Valentine would result in the production of a dextrose agglomerate and not of a calcium carbonate agglomerate. Sieving of this agglomerate, as required by the Example, would result in the calcium carbonate essentially being removed from the agglomerate. Although Example XIII has been written in the past tense, it has been shown it is unlikely that the inventors have actually performed any experiments to show how much active ingredient remains in the tablet. The language used implies that the theoretical maximum calcium carbonate content is 76.6%. As the calcium has not agglomerated, it cannot be present in such quantities. There is absolutely no reason why the person skilled in the art would use an expensive, time-consuming and complicated technique such as spray agglomeration (rather than the standard method of high speed mixing) to incorporate an active ingredient when it would result in so much wastage.

Moreover, the particle size is important for the sensoric properties and the specific surface area and crystal shape are important for the processability in a fluid bed.

### 3. Tablet samples based on agglomerates in Valentine

The Examiner states that Valentine in addition to the process also discloses tablet forms which can comprise, in addition to an active substance and a lubricant, vitamins, sweeteners and citric acid. It should be noted that there is no reference in Valentine to tablets being made based on the agglomerate of Example XIII D.

4. Product features which further distinguish the claimed invention from Valentine

Valentine specifies a tablet having a relatively hard outer shell formed from the compressed agglomerate at the tablet surface and said outer shell being relatively resistant to liquefaction when contacted with a liquid. The chewable tablet in the claimed invention does not contain such a shell and disintegrates immediately when subjected to water.

Valentine specifies that the process produces agglomerates where the bulk density is reduced by 40 to 55% of the initial carbohydrate particles. The granulates in the claimed invention on the other hand typically have a reduction of the bulk density of less than 40%.

Valentine specifies that the tablets made from agglomerates according to the process have a soft interior where the agglomerate structure is retained. The structure of the granulates according to the claimed invention on the other hand is destroyed during tablet compression due to their soft nature. Further experiments have been carried out where the a tablet is shown to disintegrate when in contact with water. The single

individual crystals of calcium carbonate are released directly from the surface of the tablet. Thus the tablet does not disintegrate into the original granules or agglomerates which shows that the granulate structure has been lost during compression. Furthermore the tablet according to the claimed invention has homogenous structure throughout the tablet with the same degree of hardness.

Agglomerates according to Valentine have a low bulk density in the range of 0.2 to 0.5 g/cc and it is stated that physical evidence shows that agglomerates formed with an active ingredient have a structure similar to that of agglomerates formed without an active ingredient. Granulates according to the claimed invention have bulk densities which typically are above 0.6 g/cc.

5. Description of the usage of surface area in Walsdorf

The Examiner states that Walsdorf teaches a calcium citrate tableting composition containing sugar, polyvinylpyrrolidone and calcium carbonate. This is somewhat misleading as the sugar, polyvinylpyrrolidone and calcium carbonate are components in the tablet coating and are not contained in the matrix of the tablet. These ingredients have thus no function with respect to acting as a calcium source, aqueous granulation binder and diluent/sweetener.

Walsdorf teaches the importance of a process for the production of calcium citrate salts with a low specific surface area in the range of 0.7 m<sup>2</sup>/g to 1.0 m<sup>2</sup>/g and with a

porous structure which makes the compactibility better than other commercial qualities. X-ray analysis showed that the calcium citrate composition of the invention had a poorer degree of crystallinity compared to commercial qualities.

Thus, the motivation for the inventor in the Walsdorf publication was to produce a calcium citrate salt which was dense and also with good compaction capability resulting in tablets with a high content of calcium citrate and a small tablet size. In order to practice the instant invention it has become essential to use calcium carbonate qualities with a low specific surface area in order to obtain a satisfactory agglomeration and short process time in a fluid bed granulation process. It must also be emphasized that the claimed invention makes use of precipitated ultra-pure crystalline qualities of calcium carbonate with clean cubic and pseudo cubic crystal shapes according to the European Pharmacopoeia.

Contrary to Walsdorf, the claimed the invention utilizes ultra-clean and non-porous qualities of calcium carbonate. The fluid bed granulation process renders these crystal particles with an excellent compactibility which has been demonstrated in high capacity tableting machines. Thus, a person skilled in the art would not look to Walsdorf in order to solve a formulation challenge, because the formulation problem was entirely different.

For the reasons stated above, the combination of Valentine and Walsdorf et al do not teach each and every element of the claimed invention nor is there any motivation to



combine these references. In short, the claimed invention is simply not made obvious by the teachings of Valentine and/or Walsdorf et al. Accordingly, the rejection of claims 1-14 under 35 U.S.C. § 103(a) is respectfully requested to be withdrawn in view of the foregoing reasons.

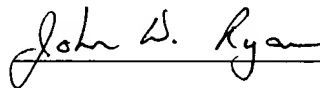
### CONCLUSION

As all of the outstanding rejections have been addressed and all of the claims are believed to be in condition for allowance, the Applicants respectfully request a Notice of Allowability upon the submission of such terminal disclaimer. The Examiner is invited to contact the undersigned representative should any further issues arise.

Respectfully submitted,

DECHERT LLP

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John W. Ryan  
Reg. No. 33,771

Dechert LLP  
1775 Eye Street, N.W.  
Washington, D.C. 20006  
Telephone (202) 261-3375  
Fax (202) 261-3333